PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Durette et al		
Serial No.:	09/086,327	Case No.: 19665Y	Art Unit:1653
Filed:	May 28, 1998		Examiner:Lukton
For:	Heterocyclic Amide Compounds as Cell Adhesion Inhibitors		

DECLARATION UNDER 37 C.F.R. 1.132

I, Richard A. Mumford, declare and state as follows:

1. I am a citizen of the United States of America residing at 62 South Street, Red Bank, New Jersey.

2. I was awarded the Bachelor of Science in Biology from the University of Masachusetts in 1971

3. I am a co-inventor of the above-identified patent application.

4. I have been employed by Merck Research Laboratories since October 3, 1975 in the department of Immunology & Inflammation, and my current title is Distinguished Senior Investigator.

5. I have been engaged in the research of VLA-4 antagonists since 1997 and I am responsible for the in vitro biological evaluation of compounds made in this project. In this role I supervise a group of 4 scientists in the in vitro testing of compounds made by the medicinal chemists.

6. I have thorough and in-depth knowledge and understanding of the in vitro assays used to screen and evaluate VLA-4 antagonists, including that described in Example 149 of the above-identified application.

7. I am a co-author of about 15 papers/presentations, and co-inventor of nine patents and patent applications, in the VLA-4 antagonist area.

8. The assay described in Example 334 of the above-identified application was conducted to evaluate the biological properties of compounds as potential VLA-4 antagonists. This in vitro binding assay measures the ability of the compounds to compete with one of the natural ligands for VLA-4, VCAM-1, in Jurkat cells. The test results are expressed as IC_{50} values in nanomolars; the IC_{50} is the concentration of test compound required to blocked 50% of the VLA-4 receptors utilizing ^{125}I-VCAM as probe.

9. The IC_{50} values for representative compounds claimed in the above-identified application are shown in ATTACHMENT A. The data indicate that compounds of the instant application are active in blocking the binding of VLA-4 expressing Jurkat cells to one of its natural ligands VCAM-1.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

By: Richard A. Mumford
Richard A. Mumford

Dated: May 6, 2004

ATTACHMENT A

Antagonism of VLA-4 Dependent Binding to VCAM-Ig Fusion Protein

{According to the Method Described in Example 334}

Ex. No.	IC_{50}, nM
(1)	58
(2)	360
(3)	257
(4)	>5000
(5)	24
(6)	>5000
(7)	29
(8)	817
(9)	6.7
(11)	>5000
(12)	>5000
(13)	2500
(14)	>5000
(19)	13
(21)	1322
(22)	4500
(24)	80
(25)	80
(26)	62
(29)	41
(30)	18
(31)	56
(32)	13
(33)	44
(34)	27

Ex. No.	IC_{50}, nM
(35)	87
(36)	2650
(37)	28
(38)	29
(39)	95
(42)	3150
(44)	73
(45)	43
(47)	33
(49)	10
(50)	27
(51)	342
(52)	166
(53)	171
(54)	3050
(55)	340
(56)	>5000
(57)	18
(58)	33
(59)	10
(62)	>5000
(64)	83
(65)	45
(66)	18
(67)	21

Ex. No.	IC_{50}, nM
(68)	41
(69)	>5000
(70)	53
(71)	150
(72)	2
(73)	0.9
(74)	1.4
(75)	3.8
(76)	35
(77)	166
(78)	2.1
(80)	0.9
(81)	0.4
(82)	0.7
(83)	1.0
(84)	0.8
(85)	0.8
(86)	0.6
(87)	3.4
(88)	0.3
(89)	98
(91)	1.9
(93)	2.4
(94)	2.2
(95)	46

Ex. No.	IC_{50}, nM
(98)	37
(100)	4.8
(101)	1.0
(102)	4.8
(104)	24
(106)	115
(107)	84
(108)	>1000
(109)	118
(110)	57
(111)	20
(112)	0.7
(113)	0.3
(114)	0.6
(115)	0.2
(116)	0.4
(117)	0.2
(118)	163
(119)	2.4
(120)	8.3
(121)	2.6
(122)	0.4
(123)	1.1
(124)	1.6
(125)	1.3
(126)	2.3
(127)	2.6
(128)	0.7
(129)	2.2

Ex. No.	IC_{50}, nM
(130)	1.9
(131)	4.6
(132)	0.13
(133)	0.13
(134)	0.6
(135)	2.0
(136)	1.0
(137)	0.3
(138)	0.5
(139)	6.6
(140)	2.8
(141)	1.0
(142)	0.9
(143)	1.5
(144)	1.4
(145)	1.0
(146)	0.8
(147)	0.5
(148)	1.3
(149)	0.7
(150)	0.3
(151)	0.7
(152)	0.4
(153)	0.9
(154)	0.5
(155)	2.4
(156)	4.8
(157)	3.2
(158)	2.3

Ex. No.	IC_{50}, nM
(159)	1.3
(160)	12
(161)	>5000
(162)	2.3
(163)	7.0
(164)	4.9
(165)	17
(166)	1.6
(167)	1.9
(168)	0.4
(169)	0.9
(170)	2.4
(171)	2.2
(172)	0.4
(173)	0.7
(174)	69
(175)	3.4
(176)	0.1
(177)	4.2
(178)	0.8
(179)	0.8
(180)	1.5
(181)	0.3
(182)	0.4
(184)	1.2
(185)	1.0
(187)	43
(188)	1.9
(190)	0.4

Ex. No.	IC_{50}, nM
(191)	0.3
(192)	9.3
(193)	0.4
(194)	0.8
(195)	2.1
(196)	0./8
(197)	0.3
(198)	103
(199)	119
(200)	15

Ex. No.	IC_{50}, nM
(201)	0.3
(202)	0.8
(203)	0.7
(204)	490
(205)	0.3
(206)	0.4
(207)	1.3
(210)	0.2
(211)	0.9
(215)	136

Ex. No.	IC_{50}, nM
(216)	0.6
(217)	6.4
(218)	2.2
(219)	2.8
(220)	0.3
(221)	1.3
(222)	10.6
(223)	1.6
(224)	2.1

Ex. No.	IC_{50}, nM
(228)	35
(229)	20
(230)	26
(231)	2.9
(232)	8.4
(233)	8.5
(234)	2.9
(235)	4.0
(236)	3.4
(237)	9.3
(238)	13
(239)	16
(240)	16
(241)	0.5
(242)	1.0
(243)	0.4
(247)	2.1

Ex. No.	IC_{50}, nM
(249)	1.8
(250)	93
(251)	2.3
(252)	1.6
(253)	2.6
(256)	8.3
(257)	1.2
(258)	3195
(259)	4.8
(261)	16
(262)	1.9
(263)	6.2
(264)	1.0
(265)	9.6
(266)	0.5
(267)	1.6
(268)	0.6

Ex. No.	IC_{50}, nM
(269)	0.4
(270)	1.8
(271)	0.5
(272)	1.3
(273)	5.8
(274)	0.4
(275)	0.2
(276)	0.6
(277)	0.3
(278)	0.4
(279)	0.3
(280)	0.7
(281)	1.6
(282)	0.1
(283)	0.2
(284)	1.9
(285)	0.3

Ex. No.	IC_{50}, nM
(286)	7.0
(287)	0.8
(288)	1.0
(290)	0.4
(291)	1.4
(292)	0.3
(293)	0.2
(294)	0.1
(295)	0.2
(296)	0.2
(297)	0.8
(298)	0.2
(299)	0.4
(300)	1.9

Ex. No.	IC_{50}, nM
(301)	1.1
(302)	0.3
(303)	0.3
(304)	0.1
(307)	0.1
(309)	0.1
(310)	0.1
(311)	0.2
(312)	0.2
(313)	0.3
(314)	0.2
(315)	81
(316)	0.4
(317)	0.2

Ex. No.	IC_{50}, nM
(318)	53
(319)	0.1
(320)	0.3
(321)	0.2
(322)	0.2
(323)	0.1
(324)	0.2
(325)	0.4
(326)	0.2
(328)	0.3
(329)	>5000
(330)	92
(331)	4560